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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,827	01/15/2004	Michael R. Rosen	13533/48003	5518

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/757,827	**Applicant(s)** ROSEN ET AL.	
	Examiner ANOOP SINGH	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 April 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *20,49,51,57,59 and 65-68*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 4/23/2010
13. ☐ Other: _____.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Continuation of 5. Applicant's reply has overcome the following rejection(s): Claims 20, 49, 51, 57, 59, 65-66 and 67-69 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 39, 65, 67-68, 73-76, of copending Application no 10/342506 (US Patent Publication no 20040137621). In view of Applicants' terminal disclaimer dated April 28, 2010, the previous rejections are rendered moot and hereby withdrawn.

The IDS filed on April 23, 2010 did not comply with the requirements of 37 CFR 1.97(d)(1) and therefore, the IDS was not considered by the Examiner.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 20, 49, 51, 57, 59, 65-68 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002), and Qu et al (Circulation res. 2001, 89:e9, IDS) for the reasons of record. Applicants' arguments filed April 21, 2010 have been fully considered but are not persuasive.

Applicants argue that Lee et al teach that invention is based on discovery that genetic modification of skeletal muscle cells to express a recombinant connexin, enables the genetically modified cells to establish electrocommunication with cardiac cells via gap junctions (col. 3, 11.28-32). Further, according to Lee, "[p]roduction of connexin in the recombinant cell provides for an electrical connection. Applicants argue that that Lee focuses on the use of skeletal muscle cells for contractility; Lee teaches that such cells should be transformed with connexins to establish electrical connections with cardiac cells (see page 7 of the arguments). Applicants further assert that Qu et al do not teach a nucleic acid encoding HCN can be delivered via mesenchymal stem cell (see page 8).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of Lee et al. to formulate the grounds for teaching away. It should be noted that the ultimate goal of expanding hematopoietic stem cells is to provide for their ultimate differentiation. As previously indicated, Lee et al teach a composition comprising a recombinant mammalian cell that is genetically engineered to express connexin 43(Cx43) protein intended for establishing electrical coupling between cardiomyocytes and recombinant mammalian cells, wherein the mammalian cells are mesenchymal stem cells. It is reported that the cell may be autologous or allogeneic to the host including human that requires transplantation of genetically modified cell (see col. 14, lines 47-55). Lee et al also teach that Cells may be autologous, allogeneic, with respect to the host. Thus, teaching of Lee embraces using human mesenchymal stem cell to treat a host that is human (see col. 14, lines 56-60, col. 5, line 21, col. 10, line 8). Additionally, Lee et al also teach a method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells which have been genetically engineered to express a connexin 43 (Cx43) protein, wherein the mammalian cells are mesenchymal stem cells (e.g. claims 1 and 2 of '644). To the extent that Lee et al. describe a composition comprising a mesenchymal stem cell that is genetically modified with a nucleic acid encoding a protein that facilitate electrical coupling between cardiomyocytes and recombinant MSC, the rejection is applicable to the instant case. The deficiency of Lee is cured by Qu who reported a composition comprising mammalian cell genetically modified to express HCN2 that shows induction expression of high current levels, with faster activation in neonate (Figures 1B and 1C) (see page 2, col. 2, para. 3). There is no requirement for Qu et al. to teach that which is clearly taught by Lee et al. It should be noted that prior art recognized that hMSC forms electrical coupling with cardiomyocytes and gene could be delivered to the heart cells or cardiomyocyte (see Lee et al supra and Wang et al J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, art of record, refernce previously applied and not relying for the instant rejection), while HCN2 over expression induced pacemaker current in mammalian heart. Applicants' selective reading of Qu et al. ignores the teachings of the primary reference of Lee et al. There is no requirement for Lee et al. to teach that which is clearly taught by Qu et al. A person of skill in the art would be motivated to express HCN2 in the recombinant MSC disclosed by Lee, because the method would allow formation of gap junction between recombinant cell and cardiac cell thereby inducing the pacemaker current in the cardiac tissue in the treatment of cardiac rhythm disorder, with a reasonable expectation of success.

Applicants further argue that Lee et al teaches away from the modification asserted in the office action because there no suggestion that other gene should encode a protein relevant to pace making. Applicants argue that Lee only suggest using nucleic acid related to achieving electrical coupling. Thus, one of ordinary skill in the art would not be motivated to combine the references. Applicants further assert that Lee specifically teaches that it is preferable to avoid additional genetic manipulation of the cells (see page 8, last para. and page 9). Applicants also argue that Qu et al do not teach any potential clinical use of HCN2, rather they are limited to explaining natural phenomena.

Such is not found persuasive, because as indicated on the record, Lee et al teach a method for treating a cardiac conduction disturbance in a host, the method comprising: introducing into cardiac tissue of said host a therapeutically effective amount of a recombinant mammalian cell genetically modified to express a connexin 43 proteins; wherein the recombinant mammalian cell is a mesenchymal stem cell, and wherein the cell is autologous or allogenic to the host, wherein said introducing is performed by injection into cardiac tissue of the host, and wherein said introducing is effective to establish an electrical connection between the recombinant cell and a myocardial cell of the host cardiac tissue; and wherein the cardiac conduction disturbance in the host is treated. Thus, among many embodiments the intended purpose of generically modifying MSC with connexin appears to also include correcting cardiac conduction disturbance (see claim 8 of Lee etal). Applicant should further note that Lee et al specifically describe that cardiac conduction disturbance include treating irregular heart beat or at least a reduction in the magnitude of a parameter such as irregular heart beat or conduction disturbances such as heart block, ventricular tachycardias or associated with congestive heart failure (i.e. lack of synchronized contraction). Thus, it is apparent from the disclosure that composition and method disclosed by Lee et al are intended for treating cardiac rhythm disorder. Given that it was known in the prior art that over expression of HCN2 in mammalian cells show induction of high current levels, it would have been obvious for one of ordinary skill in the art to either further include HCN2 gene in the composition of Lee or substitute connexin with HCN2 with reasonable expectation of success to correcting and improving the cardiac conduction disturbance in the heart. Therefore, given that HCN2 gene was routinely over expressed for improving conduction disturbance in heart by inducing pacemaker current (see Qu et al page 1108, col. 2, last two para), it would have been a matter of design choice for one of ordinary skill in the art to combine different transgene each of which is taught by the prior art to be useful for the same purpose of improving cardiac disturbance in order to produce a new composition that is to be used for the very same purpose. In the instant case the idea of combining them flows logically from their having been taught in the prior art. Thus, it would have only required routine experimentation to modify the composition and method of Lee et al to include HCN2 as disclosed Qu. Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary. It should be noted that the KSR case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of

obviousness See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). In response to applicants' argument that Lee specifically teaches that it is preferable to avoid additional genetic manipulation of the cells, it is noted that the teaching does not exclude embodiment of recombinant cell optionally modified to express other protein. Lee et al only emphasize that it is not necessary to use N-caherin as connexin alone is sufficient for the intended purpose. Applicants argument of genetically modifying cell on cardiac arrthymia has no bearing with respect to the claimed subject matter for the reasons discussed by applicant in response filed on March 7, 2006 (see page 9 and 10 of the office action).

/Anoop Singh/
Au 1632